Original Article

Common Polymorphism's Analysis of Thiopurine S-Methyltransferase *(TPMT)* in Iranian Population

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Abstract

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Objective: Thiopurine S-methyltransferase (*TPMT)* catalyses the S-methylation of thiopurine drugs. Low activity phenotypes are correlated with several mutations in the *TPMT* gene and adverse drug reactions. The molecular basis for dissimilar enzymatic activity of *TPMT* has been established in Caucasians, African-Americans and Southwest Asians, but it remains to be elucidated in Iranian population. Until present, no study on Iranian population has been performed on the known alleles of *TPMT*. The aim of this study was to investigate the frequencies of four of the most common variants of this gene.

Materials and Methods: This study was conducted during 2007 at the Department of Hematology, Tarbiat Modares University, Tehran, Iran. Using PCR-RFLP and allele specific PCR techniques, allelic variants of the *TPMT* gene *TPMT**2(G238C), *TPMT**3B (G460A), *TPMT**3C (A719G) and *TPMT**3A (G460A and A719G) were genotyped in a normal population of 127 Iranians.

Results: In this study *TPMT**2 showed a prevalence of 7.08%. *TPMT**3C and *3A were found in 2.47% and 2.18% of the samples, respectively. *TPMT**3B variant was not detected in Iranian subjects. 112 out of 127 participants showed homozygote wild type allele.

Conclusion: This study is the first to analyze *TPMT* allele frequencies in a sample of Iranian population and indicates that *TPMT**2 is the most common allele (7.08%) in this population. These results can help to organize national pretreatment strategies in patients with acute lympho blastic leukemia (ALL) or other diseases requiring thiopurine medication in their standard therapy.

Keywords: Thiopurine S-methyltransferase, Polymorphism Genetic, Pharmaco Genetics

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Introduction

Drug metabolizing enzymes participate in the neutralization of xenobiotics and biotransformation of these drugs. Polymorphisms in genes coding drug-metabolizing enzymes can alter the activity of the enzymes for their substrates (1). The anti-cancer prodrugs, 6-mercaptopurine (6-MP) and azathioprine (AZA), are metabolized by thiopurine S-methyltransferase (*TPMT)* and widely used to treat several diseases such as childhood Acute Lymphoblastic Leukemia (ALL), autoimmune hepatitis, myasthenia gravis and rheumatoid arthritis (2, 3).

Thiopurine S-methyltransferase (*TPMT*, MIM# 187680) is a cytosolic enzyme that catalyzes the S-methylation of aromatic and heterocyclic sulfhydryl compounds like 6-Mercaptopurine (6MP) (4). The *TPMT* gene is localized on chromosome 6p22.3 and consists of 10 exons. *TPMT* hypo activity is inherited as an autosomal co-dominant trait that occurs in 1/300 of general population, also it appears as homozygosity in some polymorphisms causing complete enzyme inactivity. About 10% of individuals have intermediate activity because of heterozygosity (5, 6). Some polymorphisms of *TPMT* have been shown to interfere with normal optimum activity of this enzyme and cause AZA and 6-MP toxicity.

To avoid hematotoxicity associated with *TPMT*-deficiency, phenotyping and genotyping tests should precede along with thiopurine therapy. *TPMT* molecular pharmacogenetic studies resulted in the discovery of a series of variant alleles (containing single nucleotide polymorphisms; SNPs) associated with significantly decreased levels of *TPMT* activity (3). High *TPMT* activity, results in a greater production of inactive methylated metabolites, which reduces therapeutic efficacy. Con-